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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,516	BERGERON ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 December 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-20 are pending.

2. The following new grounds of rejections are necessitated by the amendment filed 12/23/04.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 10 is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The "a histocompatibility complex protein other than HLA-DR" in Claim 10 represents a departure from the specification and the claims as originally filed. The passages pointed out by applicant in the amendment filed 12/23/05 do not provide a clear support for the said phrase. Further, the specification discloses only MHC class I. The recitation of "a histocompatibility complex protein other than HLA-DR" broadens the histocompatibility complex protein other than HLA-DR to include additional protein in addition to MHC class I.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

6. Claims 15-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "HLA-DR protein is expressed in HIV" in claims 15 and 16 is ambiguous because HIV does not expressed HIV; host HLA-DR protein *is acquired* by HIV. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

8. Claims 1-9, 11-16 and 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Dufresne et al (Biochimica et Biophysica Acta 1421: 284-294, Oct 1999; PTO 1449).

Dufresne et al teach a formulation which comprises a ligand capable of biding to HLA-DR protein such as anti-HLA-DR Fab' fragment that binds to human HLA-DR coupled to a lipid-comprising vesicle such as liposome (see entire document, abstract, page 287, Coupling reaction, in particular). The reference liposome comprises a mixture of dipalimitoylphosphatidylcholine (DPPC), dipalmitoylphosphatidylglycerol (DPPG) and dipalmitoylphosphadylethanol-amine-polyethyleneglycol (DPPE) in a molar ratio of 10: 3: 0.33 (see page 287, col. 1, in particular). The reference ratio of 10:3:0.33 is within the claimed range of 10:3:0.1-3. Claim 3 is included in this rejection because species anticipates a genus; DPPC is a species of diacylphosphatidylglycerol, while DPPG is a species of diacylphosphatidylglycerol. Further, the term "comprises" is open-ended It expands the liposome to include additional ingredient to include the reference liposome. Claim 4 is included in this rejection because the reference diacylphosphadylethanol-amine is a polyethyleneglycol derivative. The reference diacylphosphatidylcholine (DPPC): diacylphosphatidylglycerol (DPPG) molar ratio is 10:3 (see page 287, col. 1, DPPC/DPPG in a molar ratio of 10:3, in particular). The reference HLA-DR protein is expressed in a lymphoid cell such as B cells within the lymph nodes or reticuloendothelial system (see page 290, Table 1, in particular) or resting T cells (see page 291, col. 2, in particular). Claim 11 is included in this rejection because the reference formulation is intended to include drug against a disease such as HIV (see page 293, col. 1, first full paragraph, in particular). Dufresne et al teach HLA-DR protein is acquired by HIV (see paragraph bridging page 291 and 292, in particular). The reference polyethyleneglycol inherently has a molecular weight between about 500 and 5000 daltons. Thus, the reference teachings anticipate the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1, 10, 12-14, and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dufresne et al (Biochimica et Biophysica Acta 1421: 284-294, Oct 1999; PTO 1449) in view of Zelphati et al (Antisense Res Dev 3(4): 323-38, 1998; PTO 1449).

The teachings of Dufresne et al have been discussed supra. Dufresne et al teach attachment of antibodies to liposomes could be a valuable approach to combine both binding specificity of the targeting molecule to lymphocytes while reducing the accumulation of immunoliposomes at the injection site (see page 293, col. 1, in particular). The use of targeted delivery liposome as drug carriers could improve the targeting of HIV reservoirs and reduce dissemination of HIV from the lymphoid tissues (see page 293, col. 1, last paragraph, in particular).

The invention in claim 10 differs from the teachings of the reference only in that the formulation further comprises one or more proteins selected from the group consisting of major histocompatibility complex other than HLA-DR and CD4.

The invention in claims 17 and 18 differs from the teachings of the reference only in that the formulation wherein the ligand further comprises an additional ligand to one or more of CD4 and MHC-I.

Zelphati et al teach HIV acquires HLA-DR, or CD4 from host membrane protein during its life cycle. Zelphati *et al* teach a formulation for targeting an infectious agent such as HIV

wherein the reference formulation comprises immunoliposome encapsulated drug such as HIV-1 rev and tat gene-specific anti-sense phosphodiester or phosphorothioate oligonucleotides coupled to various ligands such as protein A that binds to the Fc region of antibodies to CD4 (anti-CD4 antibody BL4), and anti-HLA antibodies that bind to HLA protein on T cells (See page 328, last paragraph, page 326, first paragraph, in particular). Zelphati et al teach liposome containing anti-sense (S-anti-*rev*, n-anti-*rev* and n-anti-*tat*) targeted to HIV infected CEM cells by HLA-specific antibodies (B1.23.2) inhibited HIV-p24 expression in de novo infected cells (See page 329 last paragraph, in particular). Zelphati et al teach that CD4 molecules are effectively down modulated in chronically infected cells but the level of expression of HLA class I molecules on chronically infected cells are unaltered (See page 329, in particular). Zelphati et al teach that HLA class I molecules expressed on T cells are good target for specific delivery of liposome-encapsulated methotrexate (See page 329, in particular) and improved efficiency when drug encapsulated immunoliposomes were directed to HLA DR1 molecules expressed by targeted cells (See abstract, page 331, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the ligand such as antibodies that bind specifically to HLA class I (other than HLA-DR) and anti-CD4 as taught by Zelphati *et al* with formulation which comprises an antibody that binds specifically to HLA-DR protein coupled to liposome as taught by Dufresne et al for a formulation which comprises anti-HLA-DR that binds to HLA-DR protein coupled to a lipid comprising vesicle that further comprises additional ligands such as anti-HLA class I antibody and anti-CD4 as taught by Dufresne et al and Zelphati et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Zelphati et al teach that HLA-DR, or CD4 are acquired by HIV during its life cycle and ligand such as antibodies to HLA class I and CD4 molecules expressed on T cells are good targets for specific delivery of liposome-encapsulated drug to chronic infected T cells (see page 328, last paragraph, page 326, first paragraph, page 329, abstract, page 331, in particular). Dufresne et al teach attachment of antibodies to liposomes could be a valuable approach to combine both binding specificity of the targeting molecule to lymphocytes while reducing the accumulation of immunoliposomes at the injection site (see page 293, col. 1, in particular). The use of targeted delivery liposome as drug carriers could improve the targeting of HIV reservoirs and reduce

dissemination of HIV from the lymphoid tissues (see page 293, col. 1, last paragraph, in particular).

12. Claims 1, 12 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dufresne et al (Biochimica et Biophysica Acta 1421: 284-294, Oct 1999; PTO 1449) in view of US Pat No 5,773,027 (or record, June 30, 1998; PTO 892).

The teachings of Dufresne et al have been discussed supra. Dufresne et al teach attachment of antibodies to liposomes could be a valuable approach to combine both binding specificity of the targeting molecule to lymphocytes while reducing the accumulation of immunoliposomes at the injection site (see page 293, col. 1, in particular). The use of targeted delivery liposome as drug carriers could improve the targeting of HIV reservoirs and reduce dissemination of HIV from the lymphoid tissues (see page 293, col. 1, last paragraph, in particular).

The invention in claim 19 differs from the teachings of the reference only in that the formulation which comprises a drug wherein the drug is selected from the group consisting of AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio of 10:3 (See col. 3, liens 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine:diacylphosphatidylglycerol:diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The reference formulation further encapsulated a drug such as

AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin against the symptoms of disease caused by HIV as taught by the '027 patent with the formulation which comprises an antibody that binds to HLA-DR protein coupled to liposome as taught by Dufresne et al and the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Dufresne et al teach attachment of antibodies to liposomes could be a valuable approach to combine both binding specificity of the targeting molecule to lymphocytes while reducing the accumulation of immunoliposomes at the injection site (see page 293, col. 1, in particular). The use of targeted delivery liposome as drug carriers could improve the targeting of HIV reservoirs and reduce dissemination of HIV from the lymphoid tissues (see page 293, col. 1, last paragraph, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). The formulation which comprises encapsulated drug such as AZT, ddI, ddC,

saquinavir, ganciclovir, foscarnet and ribavirin is useful for treating HIV infection as taught by the '027 patent (See claims 7, 9-10 of '027 patent, in particular).

13. Claims 1-2 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (Antiviral Research 33: 11-20, 1996; PTO 892) in view of Catin et al (J Virology 71(3): 1922-1930, March 1997; PTO 892).

Selvam et al teach a formulation which comprises a ligand such as anti-CD4 (whole) capable of binding to CD4 wherein the reference ligand is coupled to a lipid-comprising vesicle such as liposome (See abstract, page 15, col. 1, in particular). The reference formulation comprises a drug such as 20-mer antisense DNA sequence of the rev HIV-1 regulatory gene in the form of phosphorothioate oligonucleotide against infectious agent such as HIV (see abstract, in particular). Selvam et al teach tagging liposome with anti-CD4 monoclonal antibody would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

The invention in claim 1 differs from the teachings of the reference only in that the formulation wherein the ligand is capable of binding to a HLA-DR protein instead of CD4.

Catin et al teach HIV acquired host protein such as HLA-DR, ICAM-1 (CD54), CD55 (DAF), CD59, CD63 and CD71 (see page 1922, col. 1, in particular). Catin et al teach antibody to HLA-DR or anti-LFA-1 (CD11a) inhibit HIV infection since HIV virus acquired host cellular protein on the surface of the progeny virus (see page 1922, col. 1, in particular). Catin et al teach CD4 molecule is the primary cell surface receptor for HIV-1 (page 1922, col. 2, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 (see page 1922, col. 2, in particular). The reference HLA-DR protein is expressed in lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages (see page 1922, col. 2, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ligand anti-CD4 in the anti-CD4 coupled liposome as taught by Selvam et al for the anti-HLA-DR ligand as taught by Catin et al for a formulation which comprises a ligand such as antibody that is capable of binding to a HLA-DR protein wherein the anti-HLA-DR is being coupled to a lipid-comprising vesicle as taught by Selvam et al and Catin et al. In addition, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include additional ligand to one or more proteins such as ICAM-1 (CD54),

CD55 (DAF), CD59, CD63 and CD71 as taught by Catin et al in the formulation which comprises a ligand capable of binding to a HLA-DR protein being coupled to a lipid-comprising vesicle as taught by Selvam et al and Catin et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

14. Claims 3-9 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (Antiviral Research 33: 11-20, 1996; PTO 892) in view of Catin et al (J Virology 71(3): 1922-1930, March 1997; PTO 892) as applied to claims 1-2 and 10-18 and further in view of US Pat No 5,773,027 (or record, June 30, 1998; PTO 892).

The combined teachings of Selvam et al and Catin et al have been discussed supra.

The invention in claim 3 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10: 1 and 1:1 wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length.

The invention in claim 4 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine.

The invention in claim 5 differs from the teachings of the reference only in that the formulation wherein the liposome wherein the polyethyleneglycol has a molecular weight between 500 and 5000 daltons.

The invention in claim 6 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio is 10: 3.

The invention in claim 7 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanolamine polyethyleneglycol in a molar ratio of 10:3:0.1-3.

The invention in claim 8 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3 or disterearolyphosphatidylcholine: distearoylphosphatidycholine: distearoylphosphatidylglycerol in a molar ratio of 10:3.

The invention in claim 9 differs from the teachings of the reference only in that the formulation wherein the liposome comprises a mixture of dipalmitoylphosphatidylcholine: dipalmitoylphosphatidylglycerol: dipalmitoyphophatidylethanolmine-polyethyleneglycerol in a molar ratio of 10:3:0.33 or dipalmitoylphosphatidylcholine: dipalmitolyphosphatidycholine: dipalmitoylphosphatidylglycerol in a molar ratio of 10:3:0.83.

The invention in claim 19 differs from the teachings of the reference only in that the formulation which comprises a drug wherein the drug is selected from the group consisting of AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin.

The '027 patent teaches a formulation for treatment of viral disease such as HIV which comprises a lipid vesicle or liposome that comprises a mixture of diacylphosphatidylcholine and diacylphosphatidylglycerol in a molar ratio ranging between 10:1 and 1:1, wherein the acyl chains are either saturated or unsaturated and have between 14 and 18 carbon atoms in length (palimitoyl which is 16 carbon or stearoyl which is 18 carbon in length) (See claim 1 of '027 patent, col. 3, lines 58-62, in particular). The reference formulation wherein the lipid component comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine (see claim 2 of '027 patent, in particular). The reference formulation wherein the liposome comprises a polyethyleneglycol derivative of diacylphosphatidylethanolamine and wherein the polyethyleneglycol has a molecular weight between about 500 and 5000 Daltons (See claim 11 of '027 patent, in particular). The '027 patent also teaches a formulation wherein the liposome comprises a mixture of diacylphosphatidylcholine (DPPC) and diacylphosphatidylglycerol (DSPG) in a molar ratio of 10:3 (See col. 3, liens 46-47, in particular) and a formulation wherein the lipid component comprises a mixture of diacylphosphatidylcholine: diacylphosphatidylglycerol: diacylphosphatidylethanol-amine-polyethyleneglycol in a molar ratio of 10 to 3 to 1.45 which is between the claimed 0.1-3 (See col. 5, lines 46-47, in particular). The

reference formulation further encapsulated a drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for treating viral infection (See claims 7, 9-10 of '027 patent, in particular). The '027 patent further teaches that the reference liposome formulation can be modified by coupling of antibody molecules to enhance the targeting of the liposome to the specific cells (See col. 4, lines 11-13, in particular) that are HIV reservoirs as well as marked improvement of the pharmacokinetics of drugs (See abstract, in particular). The '027 patent teaches that targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases (See col. 2, lines 25-31, col. 9, lines 7-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the liposome that coupled to a ligand capable of binding to a HLA-DR protein as taught by Selvam et al and Catin et al for the liposome with encapsulated drug such as AZT, ddI, ddC, saquinavir, ganciclovir, foscarnet and ribavirin for targeting to HIV as taught by the '027 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because not all the liposomal formulations have shown efficient drug encapsulation and drug retention and sterically stabilized liposomes have higher efficiency of drug encapsulation and drug retention by reduced leakage of entrapped drug as taught by the '027 patent (see col. 3, line 51 bridging col. 4, lines 1-27, in particular). Further, targeted delivery of anti-viral agents upon encapsulated in liposome could increase efficacy, reduce toxicity of anti-viral agents in humans suffering from AIDS or other viral diseases, improve drug bioavailability upon encapsulation of drugs into liposome that could reduce the dose of anti-viral agents used in conventional therapy as well as the frequency of administration of anti-HIV agents therefore improving the quality of life of patients with AIDS and other viral diseases as taught by the '027 patent (See col. 2, lines 25-31, col. 9, lines 7-12, in particular). HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin et al (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al

teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

15. Claims 1, 11 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selvam et al (Antiviral Research 33: 11-20, 1996; PTO 892) in view of Catin et al (J Virology 71(3): 1922-1930, March 1997; PTO 1449) and Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 626-629).

The combined teachings of Selvam et al have been discussed supra.

The invention in claim 11 differs from the teachings of the reference only in that the formulation wherein the ligand is an antibody fragment.

The invention in claim 20 differs from the teachings of the reference only in that the formulation wherein the ligand is an anti-Fab' fragment directed against HLA-DR.

Catin et al teach HIV acquired host protein such as HLA-DR, ICAM-1 (CD54), CD55 (DAF), CD59, CD63 and CD71 (see page 1922, col. 1, in particular). Catin et al teach antibody to HLA-DR or anti-LFA-1 (CD11a) inhibit HIV infection since HIV virus acquired host cellular protein on the surface of the progeny virus (see page 1922, col. 1, in particular). Catin et al teach CD4 molecule is the primary cell surface receptor for HIV-1 (page 1922, col. 2, in particular). Catin et al teach HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 (see page 1922, col. 2, in particular). The reference HLA-DR protein is expressed in lymphoid cells such as CD4+ T lymphocytes, and monocyte derived macrophages (see page 1922, col. 2, in particular).

Harlow *et al* teach a method of producing antibody fragment wherein the fragment is Fab or F(ab')2 fragment (See page 626-629, in particular). Harlow *et al* further teach that the problems of using multivalent antibodies on mammalian cells often will lead to capping and internalization of the antigen which can be overcome by using fragments of antibodies (See page 626 in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make Fab fragment thereof as taught by Harlow et al using the anti-HLA-DR as taught by Catin et al and then substituting the anti-CD4 in the anti-CD4 coupled liposome as taught by Selvam et al for a formulation which comprises a ligand capable of binding to a HLA-DR protein such as anti-HLA-DR Fab fragment being coupled to a lipid-comprising vesicle

as taught by Selvam et al, Catin et al and Harlow at al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make antibody and antibody fragment because Harlow *et al* teach that fragments of antibodies can overcome the problem of capping and internalization of the antigen on mammalian cell when using multivalent antibodies (See page 626 in particular). One having ordinary skill in the art would have been motivated to do this because HLA-DR protein is one of the most abundant host derived protein acquired by HIV-1 and HIV-2 as taught by Catin (see page 1922, col. 2, in particular) that enhances the kinetics of virus infection (see abstract, in particular). Selvam et al teach tagging liposome with antibody to host-derived molecules acquired by HIV would allow the liposomes to be targeted to a specific cell population since HIV predominantly attacks cells that bear CD4 receptor (see page 12, col. 1, last paragraph, in particular).

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 15, 2005

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